An Efficient Synthesis of *N*-Unsubstituted Imines as Organoborane Adducts Stable at Room Temperature: New Promising Intermediates for Synthesis

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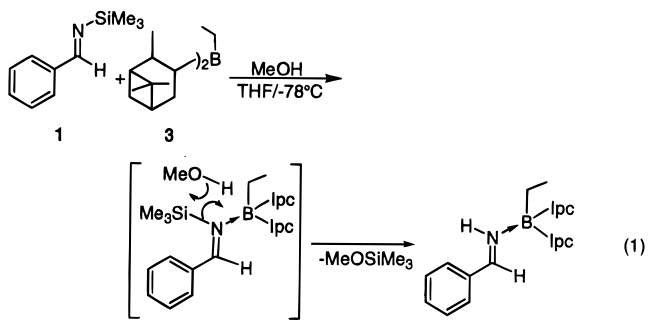
Imine chemistry has achieved a dramatic development in the past decades. Due to their importance in organic synthesis, many *N*-substituted imines have been developed and applied for the syntheses of amino acids, *β*-lactams, heterocycles, alkaloids, aziridines, and amines.[1] These include applications of *N*-sulfonyl-,[2] *N*-sulfinyl-,[3] *N*-trialkylsilyl-,[4] and other *N*-metalloimines.[5] However, these imines are most successful in the form of non-enolizable aldimines. There is still lacking a reliable, general method for generating enolizable aldimines and ketimines. Very recently, Ellman and co-workers reported a general synthesis of both non-enolizable and enolizable *N*-*tert*-butanesulfinyl imines via the condensation of *tert*-butanesulfinamide and aldehydes or ketones in the presence of excess Lewis acidic dehydrating agents. Unfortunately, these reactions can also provide a mixture of *E*- and *Z*-ketimine isomers.[6] Furthermore, difficulties in the preparation and isolation of *N*-unsubstituted imines have been well documented.[7] The access to NH aldimines has been limited to vacuum line techniques[8] and low-temperature detection.[9,10] Indeed, to the best of our knowledge, only two NH aldimines, acrylaldimine and 2-methylacrylaldimine, have ever been isolated at low temperature,[9,10] while a few more have been identified without isolation.[10] None of them could survive long enough to permit further investigation even at low temperatures. Similarly, very few NH ketimines have been isolated as single isomeric compounds.[11,12] This has greatly restricted the scope of application of imine chemistry. We herein report a general, efficient preparation of NH imines as organoborane adducts, which are single *E* isomers, stable at room temperature. This new chemistry should greatly benefit synthetic chemists, interested in utilizing imines as synthetic intermediates.

Not long ago, we reported that the allylboration of *N*-trimethylsilylbenzaldimine (**1**) with *B*-allyldiisopinocampheylborane (**2**) proceeded only in the presence of 1 molar equiv of water to give the corresponding homoallylamine in 92% ee and 90% yield.[13] Further investigation revealed that methanol can replace water in this allylboration, providing the same products. We rationalized that the reaction might have proceeded by a rapid liberation of the NH aldimine intermediate from the *N*-trimethylsilylaldimine derivative upon the addition of water or methanol, followed by a fast reaction of the NH aldimine with **2**. Although a preliminary low-temperature NMR experiment did not detect this intermediate, presumably because the allylboration of the intermediate with **2** proceeded too rapidly, we applied this methodology successfully for the synthesis of several aromatic homoallylamines in high yield and ee.[13]

Recently, we utilized a variable-temperature NMR technique for a thorough study of this reaction. To our surprise, we found that **1** does not undergo methanolysis or hydrolysis at −78 °C in deuterated THF. Even at room temperature, methanolysis of **1** in $CDCl_3$ took nearly 12 h to complete without detectable NH aldimine formation, probably due to its rapid polymerization on formation. However, in the presence of organoboranes, such as *B*-ethyldiisopinocampheylborane (**3**), the methanolysis was complete instantly and the NH benzaldimine was successfully identified at −78 °C. The ^{1}H NMR spectrum of the reaction mixture showed two doublets at 9.4 and 8.0 ppm, respectively, corresponding to the two imino-hydrogens. This observation indicated that the methanolysis or hydrolysis of *N*-trimethylsilylaldimine can be effectively initiated at −78 °C in the presence of organoboranes. Possibly, the N−Si bond is weakened by coordination of boron to the imino nitrogen, thereby becoming more susceptible to the proton-donating agents, methanol or water (eq 1).



(1)

We then examined other boron species with different Lewis acidity, including trimethyl borate (**5**), *B*-allyl-1,3,2-dioxaborinane (**6**), and *B*-methoxydiisopinocampheylborane (**7**), for the initiation of the methanolysis of **1** in CD_2Cl_2 at −78 °C. In all cases, **1** methanolized instantly with methanol and an immediate formation of the NH benzaldimine was observed by ^{1}H NMR analysis. Interestingly, we also noticed that the chemical shifts of the two imino-protons in the ^{1}H NMR spectra varied significantly with different boron compounds in the reaction. Using **5** as initiator, we observed two doublets at 9.9 and 8.7 ppm (J = 16.1 Hz, corresponding to a cis geometry of the imino-hydrogens), in contrast to 9.4 and 8.0 ppm (J = 21.0 Hz, corresponding to a trans geometry of the imino-hydrogens) using **3**. On the other hand, using **7** as the initiator, two sets of two doublets were detected in the ^{1}H NMR analysis, 9.9, 8.7 (J = 16.1 Hz) and 9.6, 8.3 ppm (J = 21.0 Hz), respectively, in a 3:2 ratio. We believe that this phenomenon probably corresponds to the presence of an equilibrium mixture of free and complexed benzaldimine (with the borane derivative) in the solution, in which the free benzaldimine's imino-proton signals showed downfield shifts at 9.9 and 8.7 ppm, while the complexed benzaldimine's imino-proton signals shifted upfield to 9.6 and 8.3 ppm. In fact, by applying a 0.5 molar equiv of **3** for the methanolysis of **1**, we detected two sets of two doublets at 9.9, 8.7 (J = 16.1 Hz) and 9.4, 8.0 ppm (J = 21.0 Hz) in a 1:1 ratio in the ^{1}H NMR analysis, in contrast to only one set of two doublets of 9.4 and 8.0 ppm (J = 21.0 Hz) observed using a 1.0 molar equiv of **3** for the same reaction. In

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that case, all the benzaldimine formed was completely complexed with **3**.[14] From the above observation, it clearly appeared to us that all the boron species initiate the methanolysis of **1**, but the more alkylated boron species tend to favor complex formation with the aldimine, because of the stronger Lewis acidity of these borane derivatives as compared to the alkoxy derivatives. We also observed that such complexation stabilizes NH benzaldimine. For example, benzaldimine generated using **3** as initiator was stable for at least 2 days at −78 °C, much longer than the earlier report,[10] while it vanished completely within 2 h when **5** was used as the initiator.

Consequently, we envisioned the preparation of imine-borane adducts stable at room temperature by implementing this new chemistry using trialkylboranes. Attempts to isolate the NH benzaldimine−**3** adduct failed. Though the aldimine was stable at −78 °C in THF, it vanished in less than 0.5 h at room temperature. The imino group was reduced by **3**, as the temperature was raised, eliminating 1 mol of α-pinene and providing benzylamine, after workup.

We were gratified, however, that employment of equimolar amounts of *B*-methyl-9-BBN (**8**) and methanol at −78 °C for the methanolysis of **1** provided the benzaldimine−*B*-methyl-9-BBN adduct (**9**) in 85% isolated yield as a yellow crystalline material. This adduct was stable at room temperature in a nitrogen atmosphere without observable alteration. To the best of our knowledge, this is the first NH aldimine−borane adduct ever isolated. Encouraged by this success, we subsequently synthesized several non-enolizable aldimine−borane adducts, such as benzaldimine−triethylborane (**10**), benzaldimine−tri-*n*-butylborane (**11**), 2-furfurylcarboxaldimine−triethylborane (**12**), and trimethylacetaldimine−triethylborane (**13**) adducts from the corresponding *N*-trimethylsilylaldimine derivatives, and isolated them in good yields via crystallization from pentane at low temperatures (Scheme S1, Supporting Information). ^{1}H NMR analysis of all the adducts revealed that only the *E* isomer formed.[14] Under an inert atmosphere, all the aldimine−borane adducts are stable at room temperature without significant decomposition for several days.

We next explored the synthesis of enolizable aldimine−borane adducts. Partial reduction of acetonitrile with diisobutylaluminum hydride (DIBAL-H) provided *N*-diisobutylaluminoacetaldimine (**14**). Treatment of this alumino-aldimine with an equimolar amount of MeOH and *B*-methyl-9-BBN furnished the desired acetaldimine-*B*-methyl-9-BBN adduct (**15**), which was formed exclusively in the (*E*)-imine form in 84% isolated yield (Scheme S2, Supporting Information). Similarly, the (*E*)-acetaldimine−triethylborane adduct (**16**) and the (*E*)-pentanaldimine−*B*-methyl-9-BBN adduct (**17**) were prepared in 71% and 83% isolated yield, respectively.

To establish a procedure for the synthesis of ketimine−borane adducts, we synthesized various *N*-trimethylsilylketimines by adopting the procedure developed by Ahlbrecht et al.[15] Thus, treatment of benzonitrile with methyllithium at −78 °C, followed by the reaction with trimethylsilyl chloride at room temperature provided *N*-trimethylsilylacetophenimine (**18**) and *N*-trimethylsilylphenylethylenamine (**19**) in a ratio of 3:7. To our satisfaction, methanolysis of this mixture with methanol in the presence of triethylborane afforded the (*E*)-acetophenimine−triethylborane adduct (**20**) exclusively in 89% isolated yield. We could not detect any enamine isomer, by ^{1}H NMR analysis, even in the crude product. Obviously, the coordination of boron to the imino-nitrogen significantly lowered the energy of the imine form, favoring its formation. Similarly, the (*E*)-3,3-dimethyl-2-butanimine−*B*-methyl-9-BBN adduct (**21**) was prepared in 78% isolated yield.

(14) In fact, **1** can be methanolyzed instantly and completely in the presence of only 5 mol % of **3** at −78 °C. The free aldimine produced, as reported previously (ref 10), is not stable even for a short period. For characterization of the *E*- and *Z*-isomer of aldimines, see ref 8.

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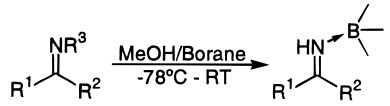
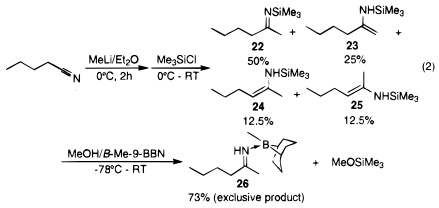
Table 1. Preparation of *N*-Unsubstituted Imine−Borane Adducts[a]



entry	R^1	R^2	R^3	borane	adduct[b]	yield (%)
1	Ph	H	$SiMe_3$	*B*-Me-9-BBN	9	85
2	Ph	H	$SiMe_3$	Et_3B	10	72
3	Ph	H	$SiMe_3$	*n*-Bu_3B	11	69
4	2-Furyl	H	$SiMe_3$	Et_3B	12	75
5	*t*-Bu	H	$SiMe_3$	Et_3B	13	70
6	CH_3	H	Al^iBu_2	*B*-Me-9-BBN	15	84
7	CH_3	H	Al^iBu_2	Et_3B	16	71
8	*n*-Bu	H	Al^iBu_2	*B*-Me-9-BBN	17	83
9	Ph	CH_3	$SiMe_3$	Et_3B	20	89
10	*t*-Bu	CH_3	$SiMe_3$	*B*-Me-9-BBN	21	78
11	*n*-Bu	CH_3	$SiMe_3$	*B*-Me-9-BBN	26	73

[a] The reactions were carried out in THF or pentane at 1 M concentration. [b] All the adducts were isolated and confirmed by ^{1}H, ^{11}B, and ^{13}C NMR and elementary analysis. Only the (*E*)-isomer was detected by 300 or 600 MHz ^{1}H NMR.

In addition, treatment of valeronitrile with methyllithium in ethyl ether at 0 °C, followed by silylation with trimethylsilyl chloride provided a mixture of *N*-trimethylsilyl-2-hexanimine (**22**), *N*-trimethylsilyl-1-hexen-2-amine (**23**), (*Z*)-*N*-trimethylsilyl-2-hexen-2-amine (**24**), and (*E*)-*N*-trimethylsilyl-2-hexen-2-amine (**25**) in a ratio of 4:2:1:1. However, methanolysis of this complicated mixture in the presence of *B*-methyl-9-BBN provided (*E*)-2-hexenimine−*B*-methyl-9-BBN adduct (**26**) solely in 73% isolated yield.[16] All the enamine isomers were converted to the more stable ketimine form (eq 2).



In summary, we have demonstrated that in the presence of trialkylboranes, *N*-trimethylsilylimines or *N*-diisobutylaluminoimines can be readily methanolyzed to afford *N*-unsubstituted imine−borane adducts as the (*E*)-isomer exclusively. The adducts can be isolated and are stable at room temperature. Using this methodology, aliphatic as well as aromatic, non-enolizable as well as enolizable, aldimine− as well as ketimine−borane adducts can be conveniently prepared.

We believe that this new class of compounds can be important intermediates for synthetic operations. In fact, our preliminary investigations revealed that the imine−organoborane adducts can be used as intermediates for the synthesis of chiral homoallylamines and β-lactams in very high yields.[17] These results will be reported subsequently.

Supporting Information Available: Schemes S1 and S2 showing the synthesis of **9**−**13** and **15**, experimental details for all procedures, the ^{1}H, ^{11}B, and ^{13}C NMR spectra of all the new imine−borane adducts, and X-ray structural information on **26** (PDF), and an X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The geometry of **26** was determined by X-ray crystallography as *E*. The variable-temperature NMR technique reveals only one isomer. The geometry of other ketimines was then determined based on the analogy.

(17) For example, asymmetric allylboration of **10** with *B*-allyldiisopinocampheylborane provides the product 1-phenyl-3-buteneamine, in 90% ee and 79% isolated yield. Further, the reaction of **10** with methyl trimethylsilyl dimethylketene acetal, in the presence of ZnI_2, followed by the addition of Grignard reagent, provides the product 3,3-dimethyl-4-phenylazetidin-2-one in 94% isolated yield.